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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/273,230	03/18/1999	JEFFREY L. CLELAND	P0998D1	6833

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/273,230	CLELAND ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,44,46,47,51 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,44,46,47,51 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: CLELAND *ET AL*

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/2006 has been entered.

2. Claims 1-41, 43,45, and 48-50 are canceled without prejudice or disclaimer.

3. Claims 42,44, 46-47, and 51-52 are pending and examined on the merits.

NEW REJECTIONS

Claim Rejections - 35 USC § 112, 1st paragraph

4. Claims 42,44, 46-47, and 51-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION. Applicant has amended the claims to recite a specific dose limitation of "80mg/ml to about 400mg/ml" of a HER2 antibody used in a method of

treating cancer. The specification as filed does not find support for the specific lower limit of 80 mg/ml. Moreover, the specification as originally filed does not support a range of 80 mg/ml to 400 mg/ml either. The specification on page 22 teaches multiple ranges, including "about 50 mg/ml to about 400mg/ml", "about 80 mg/ml to about 300mg/ml", and "about 90 mg/ml to about 150 mg/ml", however there is not specific range limitation of about 80 mg/ml to about 400 mg/ml nor is there support for 80 mg/ml to about 400 mg/ml as currently claimed. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112.

Claim Rejections - 35 USC § 112, 1st paragraph

5. Claims 42,44,46-47, and 51-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer comprising the administration of rhuMab HER2 (i.e. humanized 4D5) to subjects characterized by the over expression of HER2 receptor, does not reasonably provide enablement for a method of treating cancer comprising the administration of any and all anti-HER2 antibodies to subjects characterized by the over expression of HER2 receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of treating cancer in a subject comprising the administration of a generic class of anti-HER2 antibodies to subjects characterized by the over expression of the HER2 receptor. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims encompass the administration of broad class of HER2 antibodies. In addition, the claims also encompass a method in which a genus of antibodies that bind to other undisclosed antigens which act in a manner that inhibits the function of the HER2 receptor. For example, the claims encompass a method in which an antibody binds specifically to an intracellular portion of the HER2 receptor, but also encompass antibodies that bind to another intracellular antigen that inhibits the HER2 receptor function.

Stancovski, *et al (Proceedings of the National Academy of Science USA* **88**: 8691-8695, 1991) characterized the effects of various antibodies that bind the extracellular domain of the HER2 receptor (i.e., ErbB2), upon the growth of tumor cells.

Stancovski, *et al* teach that, while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth (page 8693, column 1). This phenomenon was also reported in Lewis *et al* (*Cancer Research* **56**: 1457-1465, 1996). Strobel *et al* (*Gynecologic Oncology* **73**: 362-367, 1999) teach discordant effects of adding two different neutralizing monoclonal antibodies to cancer cells (abstract). Despite the fact that both anti-receptor antibodies had been shown to block ligand binding to the receptor, Strobel, et al found that only one can be used effectively to block cancer cell adhesion. In light of the teachings of Stancovski, et al, Lewis, et al, and Strobel, et al, it is clear that one skilled in the art cannot predict whether an anti-HER2 receptor antibody that binds the extracellular domain of HER2 receptor will function to inhibit the growth of tumor cells *in vivo*, even if the antibody is known to inhibit an activity of the receptor (e.g., ligand binding to the receptor or dimerization with another co-receptor).

The specification fails to provide guidance that would indicate to one skilled in the art how the broadly encompassed antibodies could mediate growth inhibitory effects, but it is reasonably clear an antibody that does not bind to the extracellular domain of a particular tumor-associated antigen can not be used effectively, because the antibody will not be capable of accessing any other portion of the tumor-associated antigen and therefore cannot bind and mediate the effects of binding to a tumor cell. Furthermore, the claims encompass a method in which polyclonal antibodies are used. While polyclonal antibodies may fulfill the requirements of the claims, it is reasonably clear that polyclonal antibodies cannot be used efficaciously to treat cancer because of their

inherent lack of specificity and selectivity. Moreover, the teachings of the specification cannot be extrapolated to the enablement of the claims, because not all anti-HER2 antibodies will be therapeutically effective, resulting in the inhibition or ablation of the tumor. Likewise, not all antibodies that bind to other undisclosed antigen that inhiits the function of HER2 receptor have been disclosed or taught in the specification. One skilled in the art cannot predict which anti-HER2 antibodies can be used to successfully practice the claimed method, because one skilled in the art cannot predict what effect binding of an antibody might have upon a cell that expresses the antigen to which the antibody binds. More certainly, the skilled artisan cannot predict whether an antibody that binds an undisclosed antigen can be used to inhibit the growth of tumor cells in a patient, even if binding of the antibody to the antigen is known to inhibit the HER2 function.

The specification teaches a single embodiment within the genus of antibodies claimed (i.e. rhuMab HER2 - aka humanized 4D5), but has failed to provided any guidance with regard to other HER2 antibody which could be used effectively as the monoclonal antibody 4D5.

In the absence of exemplification that is commensurate in scope with the claims, the specification is not enabling for the use of *any* antibody that binds to the HER2 receptor or some other undisclosed antigen and thereby inhibits the HER2 function, because one skilled in the art cannot immediately practice the invention without first performing extensive and undue experimentation.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 3/7/2006.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
May 9, 2006

CHRISTOPHER YAEN
PATENT EXAMINER